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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/784,305	02/16/2001	Nickolas Papadopoulos	01107.00103	2234

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EXAMINER	
SISSON, BRADLEY L	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/784,305	PAPADOPOULOS ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 71-144* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 71-144* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Location of Application

1. The location of the subject application has changed. The subject application is now located in Workgroup 1630, Art Unit 1634.

Specification

2. The specification is objected to as documents have been improperly incorporated by reference. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Emphasis added.)

At page 17 of the response of received 27 February 2003, hereinafter response, applicant "requests that the Office specifically point to [non-patent documents that have been improperly

incorporated by reference] in its next communication." In response to this request, attention is directed to pages 15-17 of the disclosure. Found on said pages are bibliographic citations, however, such citations are not accompanied with any indication as to just hay they are being relied upon nor are they found to contain any statement that points with particularity which portion(s) is/are being incorporated by reference.

Claim Objections

3. A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim. In the present case, new claim 129 depends from claim 130, which also depends from 130 (itself).

4. A claim, which depends from a dependent claim, should not be separated by any claim, which does not also depend from said dependent claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 and 71-128 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

Claims 1, 71, 90, 109 and 128 are the only independent claims currently pending. For convenience, said claims are reproduced below.

1. (currently amended) A method of selecting ~~identifying~~ a personalized medical intervention for a non-rodent individual ~~predisposed to or having a disorder associated with at least one polymorphic marker in at least one gene or in at least one intergenic region~~, comprising the steps of:

(a) fusing cells of the non-rodent individual to rodent cell recipients to form non-rodent/rodent cell hybrids, wherein the non-rodent individual is predisposed to or has a disorder associated with at least one polymorphic marker in at least one gene or in at least one intergenic region;

(b) selecting for fused cell hybrids by selecting for a first selectable marker contained on a rodent chromosome and for a second selectable marker contained on a first non-rodent individual chromosome, to form a population of fused cell hybrids;

(c) detecting among the population of fused cell hybrids a subset of hybrids which are haploid for a second non-rodent individual chromosome which is not the same chromosome as the first non-rodent individual chromosome and which was not selected;

(d) analyzing said subset of hybrids to detect ~~a~~ the polymorphic marker in the at least one gene, in a product of the gene, or in the intergenic region, wherein the gene or intergenic region resides on the second non-rodent individual chromosome; and

(e) selecting a medical intervention for the non-rodent individual based on the presence or absence ~~identity~~ of the polymorphic marker ~~gene or intergenic region~~.

71. (currently amended) A method of ~~using a correlation between a polymorphic marker and expression or reduced expression of a gene to select~~ selecting a personalized medical intervention for a non-rodent individual, comprising the steps of:

(a) assaying a biological sample obtained from the non-rodent individual for a polymorphic marker ~~polymorphism~~ which is correlated with expression or reduced expression of a gene associated with a disorder, wherein the correlation has been determined by a method comprising the steps of:

(1) fusing cells of the non-rodent individual to rodent cell recipients to form non-rodent/rodent cell hybrids;

(2) selecting for fused cell hybrids by selecting for a first selectable marker contained on a rodent chromosome and for a second selectable marker contained on a first non-rodent individual chromosome, to form a population of fused cell hybrids;

(3) detecting among the population of fused cell hybrids a subset of hybrids which are haploid for a second non-rodent individual chromosome which is not the same chromosome as the first non-rodent individual chromosome and which was not selected;

(4) analyzing said subset of hybrids to detect a polymorphic marker in at least one gene or in at least one intergenic region, wherein the gene or intergenic region resides on the second non-rodent individual chromosome;

(5) assaying for expression of a gene on the second non-rodent individual chromosome; and

(6) identifying the polymorphic marker as correlated with expression of the gene if the subset of hybrids comprises the polymorphic marker and the gene is expressed in the hybrids or identifying the polymorphic marker as correlated with reduced expression of the gene if the subset of hybrids comprises the polymorphic marker and expression of the gene is reduced in the hybrids; and

(b) selecting a medical intervention for the non-rodent individual based on the presence or absence of the polymorphic marker in the biological sample.

90. (new) A method of selecting a personalized medical intervention for a non-rodent individual, comprising the steps of:

(a) fusing cells of the non-rodent individual to rodent cell recipients to form non-rodent/rodent cell hybrids;

(b) selecting for fused cell hybrids by selecting for a first selectable marker contained on a rodent chromosome and for a second selectable marker contained on a first non-rodent individual chromosome, to form a population of fused cell hybrids;

(c) detecting among the population of fused cell hybrids a subset of hybrids which are haploid for a second non-rodent individual chromosome which is not the same chromosome as the first non-rodent individual chromosome and which was not selected;

(d) analyzing said subset of hybrids to detect a polymorphic marker in at least one gene or in at least one intergenic region, wherein the gene or intergenic region resides on the second non-rodent individual chromosome;

(e) assaying for expression of a gene on the second non-rodent individual chromosome;

(f) identifying the polymorphic marker as correlated with expression of the gene if the subset of hybrids comprises the polymorphic marker and the gene is expressed in the hybrids or identifying the polymorphic marker as correlated with reduced expression of the gene if the subset of hybrids comprises the polymorphic marker and expression of the gene is reduced in the hybrids;

(g) assaying a biological sample obtained from the non-rodent individual for a polymorphism which is correlated with expression of a gene associated with a disorder; and

(h) selecting a medical intervention for the non-rodent individual based on the presence or absence of the polymorphic marker in the biological sample.

6. The quantity of experimentation considered to be necessary in order for one of skill in the art to reproducibly practice the full scope of the invention is on the order of many man-years with little if any expectation of success. Basis for this holding is grounded in the overwhelming lack of guidance provided.

The specification suggests that certain mammalian cells (e.g., man) can be fused with that of mice; however, the claims are not so limited. As presently worded, the claims encompass the fusing of cells from any non-rodent individual, which has been interpreted as fairly encompassing any non-rodent life form. Accordingly, the claims fairly encompassing fusing cells of a nematode with that of any rodent, e.g., that of a beaver. While claim 1, for example, requires that a first selectable marker be found in the rodent chromosome, and a second selectable marker be contained on a first non-rodent chromosome, the specification is essentially silent as to just which selectable markers are found in which rodents, much less which selectable markers are to be found in any non-rodent. As presently worded, the selectable markers do not need to be for the same condition. Case in point, the rodent chromosome may have a selectable marker for breast cancer or rheumatoid arthritis, yet such a marker would be missing from a nematode's genome, yet the nematode may well have a marker for some other condition.

7. Assuming that the rodent- and non-rodent chromosomes both have the same or similar marker, the specification does not address how one is to overcome such basic issues of having fused cells that will stably retain the non-rodent chromosome(s).

8. The specification does set forth three examples, however, all three examples a built around the fusion of human lymphocytes with that of a transformed murine cell line, E2, which originated from embryonic fibroblasts transformed with ras and adenovirus E1A oncogenes. At

page 19 of the response applicant directs attention to the aspect that "medical intervention is selected for the non-rodent individual based on the presence or absence of the polymorphic marker." It is noted with particularity that the specification is essentially silent as to how one is to interpret the results obtained from such a study and then select and initiate such medical intervention." This aspect is critical to the claimed invention and yet applicant seemingly leaves such critical steps up to the pubic to enable. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****
>
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. <u>However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.</u> It is the

> specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

In claim 1 the skilled artisan is to fuse cells of rodent and non-rodent where, as seen in step (a) the skilled artisan is already in possession of knowledge about the genetic makeup of the non-rodent cells, *i.e.*, "the non-rodent individual is predisposed to or has a disorder associated with at least one polymorphic marker in at least one gene or in at least one intergenic region." Seemingly such information is obtained in step (d) and based upon such information so obtained one is then to make a medical determination. The specification does not set forth a reproducible procedure whereby such critical information is obtained for any non-rodent individual prior to the determination of same as recited in step (d). Assuming *arguendo*, that the non-rodent individual is so predisposed to a disorder, yet the skilled artisan the specification does not enable the selection of appropriate medical intervention when the individual is diploid and is heterozygous for the polymorphic marker and wherein the other chromosome has the normal or wildtype marker and the individual is phenotypically normal. As now required in Claim 1, in such a situation, the medical treatment is to be applied even if the individual is otherwise normal. While such medical intervention is perhaps justified is the marker correlates with a dominant allele for a specific disorder, however, the same medical treatment would seemingly be applied if the individual were to exhibit a marker that correlates to a recessive disorder, meaning that both chromosomes would have to have the same defective gene(s) in order for the disorder to be expressed. As presently worded, the specification does not set forth a reproducible whereby he

skilled artisan can in a reproducible manner select appropriate medical intervention for any disorder when testing for but one marker on but one chromosome.

9. As seen in claim 7, it is not enough to select medical intervention, but one is to also provide same. The specification does not set forth a reproducible procedure whereby medical intervention has been correctly identified and provided to any non-rodent individual. At best the instant disclosure has provided but general guidance or a road map as to how such could possibly be done. Such general statements, however, do not constitute an enabling disclosure.

10. In the case of independent claim 71, the skilled artisan is to

> (4) analyzing said subset of hybrids to detect a polymorphic marker in at least one gene or in at least one intergenic region, wherein the gene or intergenic region resides on the second non-rodent individual chromosome;
>
> (5) assaying for expression of a gene on the second non-rodent individual chromosome; and

If the polymorphic marker is indeed located not in the gene but in the intergenic region, then one would not be able to assess the presence or lack of presence of the polymorphic marker as it would not be transcribed. Polymorphisms found within the coding sequence of the gene would be transcribed and could in theory be detected, however, such is not the case for polymorphisms found in introns or intergenic regions. Assuming *arguendo*, that the expression of the gene could be accomplished, a point that the Office does not concede, the specification is essentially silent as to how the skilled artisan is to interpret the data obtained and somehow select and initiate appropriate medical intervention. Similar issues of non-enablement exist with respect to independent claims 90, 109, and 128 and all dependent claims.

11. At page 21 of the response argument is presented I that the specification identifies certain specific treatments of conditions found in humans, e.g., metastatic breast cancer, Alzheimer's. As presently worded, one is to make the analysis and assignment of medical intervention without taking into consideration any clinical presentation. While such treatments may be appropriate for humans wherein the clinical presentation is taken into consideration with specific genetic analysis, the claims are not limited. It is noted with particularity that claims 13, 87, 101, 120, and 138 are directed to any dog, and claims 1-11, 14-20, 71-85, 88-99, 102-118, 121-134, and 139-144 are not limited to any particular life form other than it be "non-rodent."

12. In view of the limited guidance provided, the unpredictability in the art, the amount of experimentation required to practice the full scope of the claimed invention, one of skill would have to resort to undue experimentation. Accordingly, and in the absence of convincing evidence to the contrary, the claims are rejected under 35 USC 112, first paragraph, as not being enabled by the disclosure.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 129-144 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is noted that all of claims 129-144 depend from claim 130, including claim 130.

15. Claims 129-144 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP

§ 2172.01. The omitted steps are: any and all steps that are required to practice the claimed method. It is noted with particularity that no method steps are recited in any of the claims.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

17. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

19. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

20. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BS
June 16, 2003